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September 2, 2004

**VIA HAND**

Division of Dockets Management

FDA

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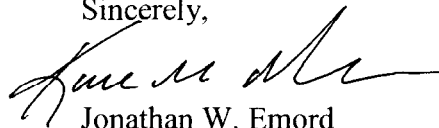
Rockville MD 20852

*Re: Glucosamine and Chondroitin Sulfate Submission*

Dear Dockets Management:

Please file the enclosed in Docket No. 2004P-0059.

Sincerely,



Jonathan W. Emord

Claudia A. Lewis-Eng

Karl M. Nobert

Enclosure

2004P-0059

SUP 8

SEP-01-2004 WED 12:17 PM EXHIBITIVE

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Sent By: EMORD &amp; ASSOC., PC;

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**An Analysis of the Conclusions Reached by the Food Advisory Committee and Dietary Supplements Subcommittee of the Food and Drug Administration on June 8, 2004**

I have examined the transcript of the June 8, 2004, combined meeting of the Food Advisory Committee and Dietary Supplements Subcommittee ("FAC") of the Food and Drug Administration (FDA), the questions the FAC was asked to consider and the conclusions reached by the FAC concerning those questions. The results of my detailed examination are described below.

**Question 1:**

**Question 1a:**

"Is joint degeneration a state of health leading to disease, i.e., a modifiable risk factor/surrogate endpoint (as discussed above) for OA risk reduction? What are the strengths and limitations of the scientific evidence on this issue?"

The FAC concluded that although joint degeneration is an aspect of osteoarthritis and represents an important phase in the continuum of transition from normal healthy to osteoarthritic cartilage, joint degeneration per se is an insufficiently specific descriptor of the anatomic and physiologic status of a joint or of articular cartilage, being present in many pathologic conditions of articular cartilage or joints, and therefore should not be considered to be a modifiable risk factor or surrogate endpoint specifically of osteoarthritis. In addition, it was concluded that joint degeneration represents an intermediate stage in the development of osteoarthritis that reflects a culmination of progressive deterioration or degeneration of the articular cartilage matrix and therefore is a manifestation of osteoarthritis rather than a risk factor that might predispose to later development of osteoarthritis.

Superficially this conclusion is consistent with the available scientific evidence when taken out of context. However, within the context of reduction of the risk for future development of osteoarthritis, the FAC was unable to exclude the possibility that the presence of joint degeneration in an individual otherwise lacking signs or symptoms of other forms of arthritis is indicative of the presence of increased risk for the future development of osteoarthritis in such an individual. Accordingly, the FAC did consider joint degeneration to be a modifiable risk factor but not exclusively or uniquely of osteoarthritis. In the context of "risk reduction," an identifiable risk factor need not be unique to any particular disease condition. To be considered to be a risk factor for osteoarthritis, joint degeneration need only be shown to be associated with increased risk for the future development of osteoarthritis in an individual. The scientific evidence made available to the FAC demonstrated such an association, as was acknowledged by the FAC during its deliberations.

**Question 1b:**

**"Is cartilage deterioration a state of health leading to disease, i.e., a modifiable risk factor/surrogate endpoint (as discussed above) for OA risk reduction? What are the strengths and limitations of the scientific evidence on this issue?"**

The FAC concluded that cartilage deterioration is a sufficiently specific descriptor of the anatomic and physiologic status of a joint or of articular cartilage leading or predisposing to future disease and could be used as a modifiable risk factor or surrogate endpoint specifically of osteoarthritis. In addition, it was concluded that cartilage deterioration can exist in a state of health (that is, the articular cartilage of members of a general healthy population – individuals without osteoarthritis – may contain one or more foci of cartilage deterioration in the absence of disease).

The FAC also concluded that joint degeneration is a manifestation of progressive cartilage deterioration, that is, unabated continuing cartilage deterioration may progress to joint degeneration. This conclusion is consistent with the available scientific evidence and suggests that cartilage deterioration may be a modifiable risk factor or surrogate endpoint of joint degeneration.

These conclusions by the FAC rely on their repeated emphasis on the place and role of cartilage deterioration in the continuum of transition from normal healthy to osteoarthritic cartilage. The support of the members of the FAC for the concept of a continuum of transition from normal healthy to osteoarthritic cartilage and for the application of its use in the interpretation of the available scientific evidence concerning modifiable risk factors and osteoarthritis was explicit, unanimous and enthusiastic.

**Question 2:****Question 2a:**

**"If we assume that joint degeneration is a modifiable risk factor/surrogate endpoint for OA risk reduction and we assume that research demonstrates that a dietary substance treats, mitigates or slows joint degeneration in patients diagnosed with OA, is it scientifically valid to use such research to suggest a reduced risk of OA in the general healthy population (i.e., individuals without OA) from consumption of the dietary substance?"**

**Question 2b:**

**"If we assume that cartilage deterioration is a modifiable risk factor/surrogate endpoint for OA risk reduction and we assume that research demonstrates that a dietary substance treats, mitigates or slows cartilage deterioration in patients diagnosed with OA, is it scientifically valid to use such research to suggest a reduced risk of OA in the general**

healthy population (i.e., individuals without OA) from consumption of the dietary substance?"

The FAC concluded in response to both of these questions that the inference that agents shown to be successful in the treatment of existing human osteoarthritis may be effective in the prevention of the development of osteoarthritis in previously-unaffected individuals is not supported by the available scientific evidence, even though the results of studies of the effectiveness of dietary agents in the treatment of existing osteoarthritis were considered to be more applicable to the predictability of the effectiveness of those dietary agents in the prevention of osteoarthritis than are the results of animal and in vitro studies.

In reaching this conclusion, the FAC contradicted their acceptance of the concept of a continuum of transition from normal healthy to osteoarthritic cartilage. However, despite having reached and expressed clear consensus in agreement with the concept of this continuum, the FAC also asserted that the metabolic character of chondrocytes within normal or deteriorating articular cartilage is fundamentally altered to the extent that the continuum is broken at an undefined transition from deteriorating cartilage to osteoarthritic cartilage. In so doing, the FAC ignored or misinterpreted a large body of evidence that was available to them that demonstrates that although the extracellular matrix of osteoarthritic articular cartilage differs biochemically and structurally from the hyaline cartilage matrix of normal unaffected cartilage, the metabolic behavior of the chondrocytes embedded within the extracellular matrix is not altered (the changes in the extracellular matrix result from normal chondrocytic responses to increases in external stimuli, such as cytokines or nitric oxide). The normality of the chondrocyte found within osteoarthritic cartilage is demonstrated by responses to stimuli that produce increases in metalloproteinase synthesis and secretion and decreases in the synthesis and secretion of cartilage-specific proteoglycans and type II collagen in chondrocytes harvested from both normal and osteoarthritic cartilage as well as in chondrocytes within tissue matrix harvested from both normal and osteoarthritic cartilage. Furthermore, abundant scientific evidence has demonstrated the similarity in metabolic responses to glucosamine and chondroitin sulfates in chondrocytes harvested from normal articular cartilage, deteriorating articular cartilage and osteoarthritic articular cartilage.

The unavoidable conclusion is that the FAC ignored or misinterpreted the available evidence in refusing to acknowledge that there is no evidence that at any time prior to the appearance of clinically-diagnosable disease the nature of the metabolic responses of chondrocytes to stimuli undergoes a change. Without a fundamental change, there is no evidence that the first clinically-apparent manifestation of human osteoarthritis results from any event other than continuation of ongoing normal responses to abnormal stimuli. In other words, the metabolic responses to abnormal stimuli that occur during one portion of the continuum (at the initial appearance of clinically-recognized osteoarthritis) are the same metabolic responses to abnormal stimuli that characterize the process of cartilage deterioration in a state of health.

On the other hand, the FAC repeatedly expressed satisfaction that the consumption of certain dietary agents has been shown to have beneficial effects on chondrocytes harvested from osteoarthritic cartilage tissue and to slow the progression of existing osteoarthritis in humans. Having drawn that conclusion, in light of the foregoing, arguing that influences of dietary agents on processes occurring during initial early clinical disease will differ from the influences of those same dietary agents on the same processes occurring in cells within tissue that has not progressed to a degree of abnormality that can be recognized by clinicians but still may be undergoing or experiencing cartilage deterioration, or that may not yet have begun to experience such deterioration, in the face of available scientific evidence to the contrary, is illogical and unscientific.

In reaching their erroneous conclusion, the FAC relied heavily on the results of a single experiment that employed a synthetic pharmacologic agent in the treatment of existing osteoarthritis and inferred that, because this drug was ineffective in preventing the appearance of osteoarthritis in supposedly previously-unaffected joints, which several FAC members demonstrated actually had not been unaffected prior to systemic drug exposure, "normal" chondrocytes (to whom the drug by design was not targeted) were in some way fundamentally different from those found in osteoarthritic tissues. This flawed line of reasoning is self-contradictory and ignored the basic tenet of pharmacologic therapeutics, which holds that synthetic compounds not found in the human body can be utilized to poison desired metabolic systems with the potential result of ameliorating existing disease conditions. Every single such agent produces "side effects" which simply reflect the inability of some cells or tissues to defend against the intentional therapeutic poisoning. In addition, the drug in question is a member of a class of drugs that includes several members (tetracycline, etc.) known to exert undesirable effects on connective tissues (especially skeletal tissues).

### Question 3:

"If human data are absent, can the results from animal and in vitro models of OA be used to demonstrate risk reduction of OA in humans?"

### Question 3a:

"To the extent that animal or in vitro models of OA may be useful, what animal models, types of evidence, and endpoints should be used to assess risk reduction of OA in humans?"

### Question 3b:

"If limited human data are available, what data should be based on human studies and what data could be based on animal and in vitro studies to determine whether the overall data are useful in assessing a reduced risk of OA in humans?"

The FAC concluded in response to these three related questions that animal studies and in vitro studies cannot replace human studies and that the value of animal studies is in hypothesis generation and in getting a better understanding of the mechanisms that might be involved in interaction between various materials and the processing of osteoarthritis. Despite drawing this conclusion, the FAC characterized the information obtained from animal models and in vitro studies as "useful," "informative," "supportive," and "part of a body of information" that provides "information about the pathogenesis of the disease" and "the place to find the biomarker" and affords "insight into individual reactions taking place, mechanistic events, and eventually an understanding of just how a process is taking place." Furthermore, the credibility of relevant animal models was acknowledged and the importance of not overlooking the portion of the available in vitro data obtained from human cells and tissues was emphasized. Despite the perceived need by the FAC to consider these three questions combined together and at face value, to their credit several members of the FAC repeatedly expressed concerns that the nature of these combined questions was inherently misleading in its attempt to preclude the requisite consideration of the totality of the available evidence when assessing the potential of a dietary substance to exhibit disease risk reduction potential.

In summary, the FAC ignored, failed to consider or contradicted the body of relevant scientific evidence that was available in its consideration of the three combined sets of questions presented by the FDA. The totality of that body of evidence clearly demonstrates that chondroprotection (inhibition of the progression of cartilage degradation and stimulation of the production of new cartilage matrix) is conferred by glucosamine and chondroitin sulfate. A dietary ingredient will exhibit a chondroprotective effect when it is demonstrated to inhibit the initiation of the metabolic events that produce the degenerative precursor lesions of osteoarthritis in hyaline cartilage composition or structure (acting, in effect, as a biological response modifier) and to support or stimulate the biosynthesis of hyaline articular cartilage matrix components that foster or are required for normal and healthy hyaline cartilage composition or structure. The chondroprotective effects of glucosamine and chondroitin sulfate occur at the metabolic, biochemical, cellular and tissue levels where they inhibit cartilage degradation and stimulate production of new cartilage matrix and are expressed both in the absence of cartilage abnormalities and in the presence of cartilage deterioration, joint degeneration, asymptomatic clinically in apparent joint disease or clinically apparent joint disease. The scientific evidence confirms that the physiological effects of glucosamine and chondroitin sulfate reflect the fundamental interactions of these dietary ingredients with the cells and matrix of hyaline articular cartilage, through which the chondroprotective effects of glucosamine and chondroitin sulfate are expressed.

The totality of available evidence, required to be considered during the evaluation of the potential for glucosamine and chondroitin sulfate to reduce the risk for cartilage deterioration, joint degeneration and osteoarthritis, leads inexorably to the conclusions that:

1. The maintenance of the biochemical, structural and functional integrity of the proteoglycan components of the extracellular matrix of articular cartilage is a required prerequisite for the preservation of healthy joint architecture and mechanical function.
2. An imbalance in cellular metabolic functions favoring catabolism within the extracellular matrix of articular cartilage compromises the biochemical, structural and functional integrity of the proteoglycan components of the extracellular matrix of articular cartilage.
3. An imbalance in cellular metabolic functions favoring catabolism within the extracellular matrix of articular cartilage produces degenerative changes in the proteoglycan composition of the matrix with net loss of healthy functioning tissue.
4. An imbalance in cellular metabolic functions favoring catabolism within the extracellular matrix of articular cartilage that compromises the structural and functional integrity of the proteoglycan components of the extracellular matrix of articular cartilage and produces degenerative changes in the proteoglycan composition of the matrix with net loss of healthy functioning tissue results in inferior biomechanical competence of affected articular cartilage with eventual structural deformation of joint architecture.
5. Net degradation of the extracellular matrix of articular cartilage, accompanied by the production of spontaneous repair matrix with abnormal proteoglycan composition, results in cartilage deterioration.
6. The progression of cartilage deterioration is required in order for abnormalities in articular cartilage composition and structure to progress to clinically apparent and symptomatic osteoarthritis.
7. The progression of cartilage deterioration to clinically apparent and symptomatic osteoarthritis is not inevitable.
8. Cartilage deterioration in the absence of joint pain represents a modifiable risk factor for later development of osteoarthritis.
9. Dietary supplementation with D-glucosamine, glucosamine-HCl, glucosamine sulfate or chondroitin sulfate contributes to the preservation of articular cartilage, inhibits the initiation of cartilage deterioration in articular cartilage and inhibits the progression of cartilage deterioration to joint degeneration, and inhibits the progression of joint degeneration to symptomatic osteoarthritis.
10. Dietary supplementation with D-glucosamine, glucosamine-HCl, glucosamine sulfate or chondroitin sulfate is an effective modifier of cartilage deterioration and reduces the risk for osteoarthritis.
11. By reducing the risk for osteoarthritis, dietary supplementation with D-glucosamine, glucosamine-HCl, glucosamine sulfate or chondroitin sulfate reduces the risk for osteoarthritis-related pain, tenderness, and swelling.

Michael J. Glade, Ph.D., F.A.C.N., C.N.S.

August 31, 2004

Reviewed and endorsed by:

CSR Bucci Date: Sep. 1, 2004  
Luke R. Bucci, PhD CCN (ASCP) CNS